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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/878,124	06/08/2001	Edward T.H. Yeh	UTSH:249US	1154

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FULBRIGHT & JAWORSKI L.L.P.
A REGISTERED LIMITED LIABILITY PARTNERSHIP
SUITE 2400
600 CONGRESS AVENUE
AUSTIN, TX 78701

EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 12/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/878,124	YEH ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,14-18,28-37 and 63-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *63-68* is/are allowed.

6)☒ Claim(s) *1-6,14-18 and 28-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 9/11/03, is acknowledged.

2. Claims 1-6, 14-18, 28-37 and 63-68 are pending and currently under examination.

3. In view of the amendment filed on 9/11/03, only the following rejections remained.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-6, 14-18, 28-37 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an *in vitro* method of screening for modulators of human C-reactive protein in serum comprising obtaining a human C-reactive protein from human serum; contacting the C-reactive protein with a candidate substance and assaying for an interaction between the C-reactive protein and the candidate substance by assaying for C-reactive protein induction of the expression of ICAM-1, VCAM or E-selectin in endothelial cells, does not reasonably provide enablement for a method of screening for modulators of a human C-reactive protein comprising obtaining a human C-reactive protein; contacting the C-reactive protein with the least a first candidate substance, assaying for an interaction between the C-reactive protein and the first candidate substance with any assay that affect the expression of any "**molecule**". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim for the same reasons set forth in the previous Office Action mailed 09/04/03.

Applicant's arguments, filed 09/11/03, have been fully considered, but have not been found convincing.

Applicant asserts that the specification provides substantial information to enable the claimed invention. Applicant points out to the specification at pages 33, line 21-page 34, line 2, and page 34 through 38.

Contrary to applicant assertion the specification does not provide sufficient enablement to determine modulation of C-reactive protein-induced expression of any "molecule".

Applicant argues that there is enablement for human C-reactive protein, *in vivo* methods, and methods that do not involve use of serum. Applicant contends that it is not necessary for the specification to provide a specific example of every C-reactive protein and every method that does not involve use of serum for the enablement requirement to be satisfied. Nor is it necessary for the specification to provided example of *in vivo* methods of the claimed invention. Applicant

contends that as long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement is satisfied.

However, results obtained under controlled conditions such as test tube *in vitro* often differ from the *in vivo* response obtained in animals. There is insufficient evidence or nexus that would lead the skilled artisan to predict the screening method for modulators of human C-reactive protein would be functional in vivo. Applicant's experimental results have relied on specific cells. It is not clear that such cells would reflect the in vivo barriers presented by all cells in an animal setting.

Applicant argues that no undue experimentation is required to practice the claimed invention. Applicant continue to argue that the specification discloses working examples, provides sufficient guidance to those of ordinary skill in the art to practice the claimed methods of screening for modulators of human C-reactive protein and not merely *in vivo* methods in serum.

Contrary to Applicant assertions, the specification discloses (page 36, lines 20-24) that the HUVEC cultured in a serum-free medium showed that incubation with 100 μg/ml of C-reactive protein could not induce adhesion molecules expression due to the inability of HUVEC to express adhesion molecules in the absence of serum. The specification further discloses that the effects of CRP are dependent on the presence of serum. Furthermore, the specification discloses that CRP effects are dependent on one or more serum co-factors (page 36, lines 25-26). The specification must contain sufficient technical information to describe the claimed invention to a person of ordinary skill in the art to which the claimed invention pertains and to enable such a person to make and use the claimed subject matter, without requiring undue experimentation. Thus, given the lack of data on in vivo method of screening for modulators of human C-reactive protein, for one of skill in the art to practice the invention as claimed would require a level of experimentation that is excessive and undue.

6. Claims 1-6, 14-18 and 28-37 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons set forth in the previous Office Action mailed 09/04/03.

Applicant's arguments, filed 09/11/03, have been fully considered, but have not been found convincing.

Applicant traverses the rejection based on the ground that the evidence for the written description support can be found throughout the entire specification. Applicant contends that the specification provides adequate written description support for human C-reactive protein as well as for *in vivo* methods and for methods that do not involve the use of serum. Applicant further points to example 1 in the specification which provides information pertaining to HUVEC cell

culture and general information pertaining to C-reactive protein. Applicant further contends that example 2 provides details pertaining to how to conduct the claimed screening methods and provides guidance which can be applied in both in vitro and in vivo screening methods. Applicant asserts that the specification provides information pertaining to measurement of the induction of an adhesion molecule, a receptor, a signaling molecule, a cytokine, or an enzyme in the presence of serum.

However, there is no described or art-recognized correlation or relationship between the structure of the invention, the human C-reactive protein and it's modulation function, the feature deemed essential to the instant invention. Therefore, one of skill in the art would not envisage, based on the instant disclosure, the claimed genus of molecules and adhesion molecules.

7. The following new ground of rejections is necessitated by the IDS submitted 9/11/03.

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-2, 4, 6, 14 and 32 stand rejected under 35 U.S.C. 103(a) as being obvious over Tseng *et al* (Mol. Immuno. 25:679-686, 1988).

Tseng et al teach a method of screening for modulators of C-reactive protein (CRP) comprising obtaining CRP from human ascites fluids (see abstract and page 680, under Purification of CRP in particular), contacting the CRP with different mAb such as mAbs to CRP that bind at or near the PC-binding site and mAb to the mouse PC-binding idiotype T-15, which also reacts with the PC-binding site of CRP and assaying for an interaction the % inhibition of CRP binding determined on the basis of CRP bound to Fn in the absence of mAb (see Table 2 on page 683 in particular). Tseng *et al* further teach mAb to the mouse PC-binding idiotype T-15 inhibits the binding of CRP to Fn. Tseng *et al* further teach that CRP binds with high affinity to purified plasm fibronectin (Fn) when the Fn is immobilized on a surface or matrix via either specific IgG antibody or by gelatin (see abstract and figure 1 in particular), wherein the binding enhances adhesion (see page 685 last paragraph in particular).

The claimed invention differs from the reference teaching only by the recitation that the antibody modulates C-reactive protein-induced expression of a molecule in claim 1.

While Tseng et al do not expressly teach that the monoclonal antibodies modulate the expression of an adhesion molecule, it is immediately apparent the antibody would modulate the adhesion molecule.

Geving the biological significance of the CRP to Fn binding would alter the cell attachment, one of ordinary skill in the art at the time the invention was made would have been motivated to to determine the modulates C-reactive protein-induced expression of these adhesion molecules in a method of screening for modulators of human C-reactive protein.

Form the combined teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments, filed 09/11/03, have been fully considered, but have not been found convincing.

Applicant argues that Tseng et al fail to anticipate the claimed invention because the reference neither expressly or inherently teach the limitation "assaying for an interaction between the V-reactive protein and the first candidate substance with an assay that determines modulation of C-reactive protein-induced expression of a molecule relative to C-reactive protein-induced expression of a molecule relative to protein with the disclosed monoclonal antibodies.

However, geving the biological significance of the CRP to Fn binding would alter the cell attachment, one of ordinary skill in the art at the time the invention was made would have been motivated to to determine the modulates C-reactive protein-induced expression of these adhesion molecules in a method of screening for modulators of human C-reactive protein with resonable expection of success.

10. Claims 1-4, 6, 14, 28 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cermak *et al* (Blood 82:855-860, 1993 (IDS Ref. No. C3)), in view of Marx *et al* (Circulation 98(9):906-911, September 1998).

Cermak *et al* teach a method of screening for modulators of C-reactive protein (CRP) comprising contacting human CRP with tissue factor (TF) and assaying for the production of CRP. Cermak *et al* further teach that TF led to increased production of C-reactive protein. Cermak *et al* further teach that CRP-induced production was completely blocked by a monoclonal antibody against human TF but not by irrelevant murine IgG. Furthermore, Actinomycin D, cycloheximide and anti-human CRP IgG inhibited CRP-induced PCA production blocked CRP-stimulated

production (see abstract, page 513 in particular). Cermak *et al* teach that the incubation times was carried out in RPMI 1640 and 1% FCS.

The claimed invention differs from the reference teaching only by the recitation that assaying for an interaction between the C-reactive protein and the first candidate substance with an assay that determines modulation of C-reactive protein and first candidate substance with an assay that determines modulation of C-reactive-induced expression of a molecule relative to C-reactive protein-induced expression of the molecule in the absence of the first candidate substance, and determining whether any modulation of C-reactive protein induced expression of the molecule occurs in claim 1,

Marx et al teach that the increase in monocyte PCA has to be attributed to TF activity, because the observed effects were absent in factor VII-deficient plasma and could be inhibited by the addition of blocking anti-TF Mabs (see page 910, 1st col., 2nd paragraph in particular). Marx *et al* teach that the mechanism involves de nove protein synthesis (see page 910, 1st col., 3rd paragraph). Finally, Marx *et al* teach the enhancement of monocyte PCA is an effect of β2-integrin/ICAM binding (see page 911, last paragraph in particular) and ICAM-1 has an important role in the cellular adhesion molecules for PCA induction (see page 911, 1st col., 4th paragraph in particular).

Geving the the PCA is mediated by intercellular adhesion molecule-1, it would have been obvious to one of ordinary skill in the art at the time the invention was made to assay for the ICAM adhesion molecule in a method of screening for a modulators of human C-reactive protein comprising contacting human CRP with TF and assaying for ICAM adhesion molecule taught by Marx et al instead of the production of CRP taught by Cermak et al. Further, it is immediately apparent that Cermak *et al* determined the production of CRP induced synthesis relative to CRP a control in the absent of CRP.

One of ordinary skill in the art at the time the invention was made would have been motivated to to do so because ICAM-1 has an important role in the cellular adhesion molecules for PCA induction as taught by Marx et al reference.

Form the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

11. Claims 15-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cermak *et al* (Blood 82:855-860, 1993 (IDS Ref. No. C3)), in view of Marx *et al* (Circulation 98(9):906-911, September 1998), as applied to claims 1-4, 6, 14, 28 and 32 above, and further in view of U.S. Patent No. 6,455,046 (of Record).

The Marx *et al* and Cermak *et al* references have been discussed, supra.

The claimed invention differs from the reference teaching only by the recitation that the C-reactive protein is procured by isolation from a cell recited in claim 15, wherein the cell comprises a recombinant nucleic acid sequence encoding a C-reactive protein and C-reactive protein is expressed from the recombinant nucleic acid sequence in claim 16, wherein C-reactive protein is isolated from serum in claim 17, and wherein the serum is human serum in claim 18.

The '046 patent teaches that the native CRP can be obtained from natural sources (e.g., serum, plasma, pleural fluid or ascites fluid). The '046 patent teaches that native CRP can also be produced by recombinant DNA techniques. Genomic and cDNA clones coding for human, mouse, and rabbit CRP have been isolated and sequenced. The '046 patent teaches to obtain native CRP, eukaryotic host cells, preferably mammalian host cells, should be used for the expression of the CRP clone. Finally, the '046 patent teaches that using those isolation methods, CRP can be obtained which is about 99% pure (see column 2, line 67 and column 3, lines 1-48 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to obtain the C-reactive protein taught by Cermak et al from a cell, a recombinant DNA techniques, or human serum as taught by '046 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to to do so because using those isolation methods provides 99% pure CRP as taught by the '046 patent.

Form the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

13. Claims 63-68 are allowable.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 872-9307.

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600
November 24, 2003

Christina Chan

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600